BY CHARLES J. DUNTON, MD

Excisional biopsy for CIN

Thanks to technological improvements, LEEP has become the most common excisional technique for squamous dysplasia, although cold-knife conization is preferred when invasive disease is suspected. An expert reviews indications and recommends operative and follow-up strategies.

When cervical intraepithelial neoplasia (CIN) requires treatment, loop electrosurgical excision procedure (LEEP) is the most frequently used modality, although cold-knife conization (CKC) of the cervical transformation zone still is preferred in select cases. Since excisional techniques are used with CKC, margin status is known and clinical decisions may be based on this information.

This article reviews current indications for excisional biopsy and presents evidence to direct management and follow-up of patients with positive and negative margins.

KEY POINTS

- In most cases, loop electrosurgical excision procedure (LEEP) and cold-knife conization (CKC) result in equivalent success rates and margin status.
- CKC is preferred in cases of adenocarcinoma in situ or squamous microinvasion.
- Conservative follow-up is generally possible in adenocarcinoma in situ and squamous microinvasion when margins are negative.
- Colposcopy, endocervical curettage, and biopsies should be part of the follow-up strategy for patients with positive margins.

Selecting a technique

Several large randomized and prospective studies have demonstrated that LEEP is similar in efficacy to CKC and may even remove less of the normal cervical stroma.[1-3] In general, LEEP is used to excise high-grade and recurrent squamous dysplasia, as it is similar to CKC in its rates of incomplete excision and residual disease.[1,4] However, when adenocarcinoma in situ (AIS) is present, CKC is preferred for diagnosis and treatment, since it results in a lower incidence of involved margins and a lower recurrence rate.[3,5-7]

CKC also is preferred when histologic confirmation of the margin status is crucial, such as when invasion with squamous lesions is suspected. This is because thermal artifacts

CONTINUED

▪ *Dr. Dunton is director of the division of gynecologic oncology at Albert Einstein Medical Center in Philadelphia.*

that may result from LEEP will interfere with interpretation, further complicating treatment planning.[1,4,8,9] In cases of microinvasion, the ability to confirm margins makes conservative treatment possible; if the depth of invasion cannot be determined from the specimen, radical surgery may be necessary.

In the hands of an experienced clinician, however, thermal artifact from the LEEP technique generally is not a significant problem. Series reporting high rates of uninterpretable margins have been attributed to operator inexperience.[10] In general, thermal artifact is reduced by limiting the number of sections taken. In ideal cases, only a single-piece specimen is obtained, similar to that achieved using CKC.[8,10,11] Newer loops, such as the cone biopsy excision loop, may decrease the number of sections and further improve margin interpretation.[8]

I use CKC in cases of suspected squamous invasion and in the evaluation of glandular lesions, but feel that in other cases LEEP is efficacious and quicker.

Residual disease and margin status: squamous dysplasia

AUTHOR	PROPORTION WITH RESIDUAL DISEASE			
	NEGATIVE MARGINS		POSITIVE MARGINS	
	NUMBER	%	NUMBER	%
SQUAMOUS LESIONS				
Bertelsen et al, 1999[23]	44/485	9	29/76	38.2
Moore et al, 1995[24]	170/523	32.5	37/91	40.7
Lopes et al, 1993[25]	0/176	0	11/131	8.4
Murdoch et al, 1992[26]	7/405	1.7	22/160	13.8
Andersen et al, 1990[19]	0/411	0	6/469	1.3
TOTALS	221/2,000	11	105/927	11.3
SQUAMOUS MICROINVASION				
Gurgel et al, 1997[27]	6/74	8.1	45/76	59.2
Roman et al, 1997[22]	1/30	3.3	7/50	14
TOTALS	7/104	6.7	52/126	41.3

Identifying residual disease

When both the endocervical margin and endocervical curettage (ECC) are positive for squamous dysplasia at the time of excision, there is an increased risk of residual disease (**TABLE 1**).[12-14] However, it is not clear whether ECC alone is an independent predictor of residual disease. Although 1 study suggests an increased risk of invasive cancer in women over 50 years of age with a positive ECC at the time of conization, other series have failed to demonstrate a difference in treatment failure rates based on ECC.[15-17] Thus, the utility of ECC in directing further therapy at the time of excisional biopsy is unclear. I generally do not perform an ECC with LEEP for squamous dysplasia.

In AIS, a positive ECC is a strong predictor of residual disease, while a negative ECC is of limited significance.[18] I am more likely to perform an ECC with glandular lesions. If it is negative, close follow-up still is indicated. If it is positive, repeat excision may be necessary.

Follow-up of squamous lesions

Considerable clinical uncertainty remains over the relative strengths of cytologic, colposcopic, and histologic evaluation for residual or recurrent disease following excisional biopsy. Conservative management includes Papanicolaou smears alone or in combination with ECC and/or colposcopy.

Negative margins. If margins are negative, the success rate of excisional biopsy is high (90%-100%), and careful observation is the preferred follow-up. Repeat cytologic testing

CONTINUED

will identify the majority of patients with residual high-grade disease. A prospective randomized trial of cytologic surveillance showed that the detection rate was only 1.9% higher for histology.[19] Although 1 report suggests that colposcopy can expedite the diagnosis of recurrent dysplasia, it is unclear from this report whether colposcopy identified significant high-grade dysplasia that cytology missed.[20]

Positive margins. In most series involving CIN with positive margins, treatment success rates do not differ significantly between patients who undergo repeat surgical procedures and those who have close follow-up. However, endocervical margin involvement appears to carry a higher treatment failure rate than ectocervical margin involvement. Data are conflicting on the proper method of conservative follow-up. Some authors propose only frequent cytologic testing, while others recommend that colposcopy be performed.[19-21]

There is a **significant risk** of residual disease or **true invasion** when margins or an ECC are positive and microinvasion is present.

For patients with positive margins, I perform both cytology and colposcopy in 4 to 6 months. If an endocervical margin was positive, I also perform an ECC. If this evaluation is negative, I repeat cytologic testing every 6 months until 3 consecutive Pap smears are normal and satisfactory. In cases of recurrent high-grade dysplasia with positive margins, hysterectomy may be indicated, depending on the patient's age and desire for continued fertility.[14,21]

Squamous microinvasion

There is a significant risk (50%-80%) of residual disease or true invasion when margins or an ECC are positive and microinvasion is present.[2,5-7] In these cases, a repeat excisional biopsy should be performed to determine the true extent of disease prior to deciding on definitive therapy.[22] As previously mentioned, CKC is preferred to limit artifact that could obscure interpretation. If the patient has completed her childbearing, hysterectomy remains the standard treatment for microinvasive squamous cell carcinoma. When the woman wishes to preserve fertility, conservative follow-up appears to be safe if the final pathologic specimen has negative margins. A follow-up protocol including cytologic, colposcopic, and ECC monitoring in the first post-conization visit is recommended.[2,6]

Glandular lesions

AIS with involved margins requires further surgery due to the possibility of residual AIS or invasion (TABLES 2 and 3).[2,5-7] In these cases, CKC is preferable to LEEP.[3,5-7] Hysterectomy remains the standard therapy for AIS. Conservative management is an option if fertility is desired and margin status is negative. Patients should be informed that persistent disease or recurrence is possible and that there is a risk of invasive disease.[15]

CONTINUED

Residual disease and margin status: adenocarcinoma in situ

AUTHOR	PROPORTION WITH RESIDUAL DISEASE			
	NEGATIVE MARGINS		POSITIVE MARGINS	
	NUMBER	%	NUMBER	%
Azodi et al, 1999[28]	5/16	31.3	9/16	56.3
Goldstein et al, 1998[18]	13/43	30.2	8/18	44.4
Denehy et al, 1997[6]	2/7	28.6	7/10	70
Widrich et al, 1996[5]	0/3	0	9/14	64.3
Wolf et al, 1996[29]	7/21	33.3	10/19	52.6
TOTAL	27/90	30	43/77	55.8

TABLE 3

Follow-up recommendations

Pathology	Margin status	Recommendation
High-grade squamous lesion	Negative	• Repeat cytology every 6 months until 3 consecutive Pap smears are normal and satisfactory • Colposcopy and directed biopsy for any abnormality
	Positive, endocervical	• Colposcopy, cytology, and ECC at 4 months; then repeat cytology every 6 months until 3 consecutive Pap smears are normal and satisfactory • Colposcopy and directed biopsy for any abnormality
	Positive, ectocervical	• Colposcopy, cytology at 4 months (ECC if unsatisfactory examination); then repeat cytology every 6 months until 3 consecutive Pap smears are normal and satisfactory • Colposcopy and directed biopsy for any abnormality
Squamous microinvasion	Negative, fertility desired	• Colposcopy, cytology, and ECC at 4 months; then repeat cytology and colposcopy every 6 months until 3 consecutive Pap smears are normal and satisfactory • Directed biopsy and ECC for any abnormality
	Negative, no desire for fertility	Hysterectomy
	Positive	CKC
Adenocarcinoma in situ	Negative, fertility desired	• Colposcopy, cytology, and ECC at 4 months; then repeat cytology every 6 months until 3 consecutive Pap smears are normal and satisfactory • Colposcopy and directed biopsy for any abnormality
	Negative, no desire for fertility	Hysterectomy
	Positive	CKC

CKC = cold-knife conization; ECC = endocervical curettage

CONTINUED

Counseling, thorough documentation, and second surgical and pathologic opinions may be helpful in conservative management. Colposcopy, ECC, and cytology are indicated at the first follow-up visit, with cytology repeated every 6 months until 4 consecutive Paps are normal. More frequent colposcopy and liberal use of ECC also may be considered.

When further excision is necessary

As noted earlier, repeat excision is necessary in cases of squamous microinvasion or AIS with positive margins. CKC is generally preferred to allow for optimal pathologic interpretation. For squamous intraepithelial lesions, excisional biopsy with close follow-up has a significant cure rate, and hysterectomy usually is not indicated. However, hysterectomy still should be considered part of the treatment continuum for CIN, particularly for patients who have completed childbearing.

Conclusion

Although the risk of recurrence is correlated with a patient's margin status in cases of squamous dysplasia, conservative follow-up is possible and has a high success rate. Cytology is sufficient surveillance for cases involving negative margins. When margins are positive, colposcopy and ECC also may be useful. Microinvasive lesions with positive margins require further surgical evaluation to determine treatment. For glandular lesions, CKC is preferred for both diagnosis and treatment. ■

REFERENCES

1. Mathevet P, Dargent D, Roy M, Beau G. A randomized prospective study comparing three techniques of conization: cold knife, laser, and LEEP. *Gynecol Oncol*. 1994;54(2):175-179.
2. Duggan BD, Felix JC, Muderspach LI, et al. Cold-knife conization versus conization by the loop electrosurgical excision procedure: a randomized, prospective study. *Am J Obstet Gynecol.* 1999;180:276-282.
3. Girardi F, Heydarfadi M, Koroschetz F, et al. Cold-knife conization versus loop excision: histopathologic and clinical results of a randomized trial. *Gynecol Oncol.* 1994;55:368-370.
4. Gold M, Dunton CJ, Murray J, et al. Loop electrocautery excisional procedure: therapeutic effectiveness as an ablation and a conization equivalent. *Gynecol Oncol*. 1996;61:241-244.
5. Widrich T, Kennedy AW, Myers TM, et al. Adenocarcinoma in situ of the uterine cervix: management and outcome. *Gynecol Oncol.* 1996;61:304-308.
6. Denehy TR, Gregori CA, Breen JL. Endocervical curettage, cone margins, and residual adenocarcinoma in situ of the cervix. *Obstet Gynecol.* 1997;90:1-6.
7. Muntz HG, Bell DA, Lage JM, et al. Adenocarcinoma in situ of the uterine cervix. *Obstet Gynecol.* 1992;80:935-939.
8. Naumann RW, Bell MC, Alvarez RD, et al. LLETZ is an acceptable alternative to diagnostic cold-knife conization. *Gynecol Oncol.* 1994;55:224-228.
9. Eddy GL, Spiegel GW, Creasman WT. Adverse effect of electrosurgical loop excision on assignment of FIGO stage in cervical cancer: report of two cases. *Gynecol Oncol*. 1994;55:313-317.
10. Montz FJ, Holschneider CH, Thompson LDR. Large-loop excision of the transformation zone: effect on the pathologic interpretation of resection margins. *Obstet Gynecol*. 1993;81:976-982.
11. Gardeil F, Barry-Walsh C, Prendiville W, et al. Persistent intraepithelial neoplasia after excision for cervical intraepithelial neoplasia grade III. *Obstet Gynecol*. 1987;89:419-422.
12. Felix JC, Muderspach LI, Duggan BD, Roman LD. The significance of positive margins in loop electrosurgical cone biopsies. *Obstet Gynecol.* 1994;84:996-1000.
13. Kobak WH, Roman LD, Felix JC, et al. The role of endocervical curettage at cervical conization for high-grade dysplasia. *Obstet Gynecol*. 1995;85:197-201.
14. Husseinzadeh N, Shbara I, Wessler T. Predictive value of cone margins and post-cone endocervical curettage with residual disease in subsequent hysterectomy. *Gynecol Oncol.* 1989;33:198-200.
15. Poyner EA, Barakat RR, Hoskins WJ. Management and follow-up of patients with adenocarcinoma in situ of the uterine cervix. *Gynecol Oncol.* 1995;57:158-164.
16. Frauchiger WL, De Frias DVS, Cajulis RS, Yu GH. The immediate postconization endocervical smear: evaluation of its utility in the detection of residual dysplasia. *Acta Cytol*. 1998;42:1139-1143.
17. Wright TC, Gagnon S, Richart RM, Ferenczy A. Treatment of cervical intraepithelial neoplasia using the loop electrosurgical excision procedure. *Obstet Gynecol*. 1992;79:173-178.
18. Goldstein NS, Mani A. The status and distance of cone biopsy margins as a predictor of excision adequacy for endocervical adenocarcinoma in situ. *Am J Clin Pathol*. 1998;109:727-732.
19. Andersen ES, Nielsen K, Larsen G. Laser conization: follow-up in patients with cervical intraepithelial neoplasia in the cone margin. *Gynecol Oncol.* 1990;39:328-331.
20. Paraskevaidis E, Jandial L, Mann EMF, Fisher PM. Pattern of treatment failure following laser for cervical intraepithelial neoplasia: implications for follow-up protocol. *Obstet Gynecol*. 1991;78:80-83.
21. Lapaquette TK, Dinh TV, Hannigan EV, et al. Management of patients with positive margins after cervical conization. *Obstet Gynecol*. 1993;82:440-443.
22. Roman LD, Felix JC, Muderspach LI, et al. Risk of residual invasive disease in women with microinvasive squamous cancer in a conization specimen. *Obstet Gynecol.* 1997;90:759-764.
23. Bertelsen B, Tande T, Sandvei, Hartveit F. Laser conization of cervical intraepithelial neoplasia grade 3. *Acta Obstet Gynecol Scand.* 1999;78:54-59.
24. Moore BC, Higgins RV, Laurent SL, et al. Predictive factors from cold knife conization for residual cervical intraepithelial neoplasia in subsequent hysterectomy. *Am J Obstet Gynecol.* 1995;173:361-368.
25. Lopes A, Morgan P, Murdoch J, et al. The case for conservative management of "incomplete excision" of CIN after laser conization. *Gynecol Oncol.* 1993;49:247-249.
26. Murdoch JB, Morgan PR, Lopes A, Monaghan JM. Histological incomplete excision of CIN after large loop excision of the transformation zone (LLETZ) merits careful follow up, not retreatment. *Br J Obstet Gynaecol.* 1992;99:990-993.
27. Gurgel MSC, Bedone AJ, Andrade LA, et al. Microinvasive carcinoma of the uterine cervix: histological findings on cone specimens related to residual neoplasia on hysterectomy. *Gynecol Oncol.* 1997;65:437-440.
28. Azodi M, Chambers SK, Rutherford TJ, et al. Adenocarcinoma in situ of the cervix: management and outcome. *Gynecol Oncol.* 1999;73:348-353.
29. Wolf JK, Levenback C, Malpica A, et al. Adenocarcinoma in situ of the cervix: significance of cone biopsy margins. *Obstet Gynecol.* 1996;88:82-86.

Dr. Dunton reports no affiliation or financial arrangement with any of the companies that manufacture drugs or devices in any of the product classes mentioned in this article.